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LHRH - ANTAGONISTS IN THE TREATMENT
OF FERTILITY DISORDERS

Cross references to Related Applications

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This application is based on provisional application serial No. 60/011,282 filed February 7, 1996, the content of which is incorporated herein by reference.

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Field of the Invention

The field of invention is directed to the use of LHRH-antagonists to
15 treat male and female fertility disorders.

Background of the Invention

The reasons for unsuccessful attempts to establish pregnancy can be
20 attributed equally to male and female fertility disorders. Today many
different assisted reproduction techniques are available. These techniques
are used to induce multiple and synchronous follicular growth and thereby
obtain fertilizable oocytes.

The current standard treatment is to induce multiple follicular
25 development by administering high doses of HMG (Human Menopausal
Gonadotropin). This results in ovarian hyperstimulation. Upon reaching a
suitable degree of oocyte maturation using these techniques, ovulation is
induced by the administration of HCG (Human Chorion-Gonadotropin) in
order to obtain a sufficient number of oocytes. During this time, the clinic-
30 infrastructure preparation can begin. Preparation includes recovery of
oocytes by abdominal or transvaginal puncture, intracorporal or
extracorporal fertilization of oocytes by different techniques and embryo
replacement into the uterus. Routinely, beginning pregnancy is supported
by additional administrations of HCG or progesterone. Today this

treatment is applied to clinical conditions of male and female infertility.

Complications that are frequently observed during the hyperstimulation procedure are:

A: premature surges of luteinizing hormone (LH) at a premature
5 maturation state with a rupture of the follicles that induced a subsequent
cancellation of the treatment occurring in about 25% of the patients; and B:
ovarian hyperstimulation syndromes induced by exogenous gonadotropins
which in severe cases require hospitalization and are life-threatening.

In order to avoid premature LH-surges, today LHRH-agonists are
10 used as a comedication. By continued administration of these drugs, a
complete suppression of endogenous gonadotropins is achieved by
desensitization of pituitary cells and down-regulation of their receptors.
Subsequently, the gonadotropin levels can be controlled by exogenous
injection and the pituitary is refractory to the stimulation of LH-release by
15 increasing levels of estradiol. Disadvantages are 1) a long treatment period
until the suppression and down-regulation occur; 2) estrogen withdrawal
symptoms; 3) disturbance of the normal menstrual cycle; 4) the need for
frequent hormone determinations in order to evaluate the time of onset of
suppression; and 5) high dose HMG treatment is needed for ovarian
20 stimulation.

The pathogenesis of hyperstimulation syndrome is not completely
understood, but is thought to be associated with the use of HCG for
ovulation induction and luteal phase support.

One recent approach involves the use of the LHRH antagonist
25 Cetrorelix (INN). In first clinical trials, short term treatment with
Cetrorelix resulted in a complete avoidance of premature LH surges during
stimulated cycles and the need for HMG. Due to the immediate

suppression of gonadotropins by this antagonist, the unwanted stimulatory phase and also the withdrawal of estrogen produced by the agonists was avoided. The duration of treatment was also significantly shortened. In addition, it was shown that a single injection of an antagonist, given in the
5 mid-follicular phase, would adequately suppress premature LH surges.

SUMMARY OF THE INVENTION

Despite the improvements described above, these treatment modalities suffered the drawback of treating the patients with the highest
10 possible dose of exogenous gonadotropins to hyperstimulate multiple follicular development which results in some severe adverse events.

The current invention reduces the severe adverse events, improves patient compliance and reduces costs. Recent data obtained with Cetrorelix also demonstrates additional surprising new advantages for the treatment of
15 male and female infertility.

In animal experiments and clinical studies with Cetrorelix, it was possible to induce an arrest of the normal, unstimulated follicular growth by multiple or single injections. These effects were observed with extremely low dosage levels. These low dosage levels present new
20 possibilities for manipulating the time of ovulation during a normal, not exogenous gonadotropin-stimulated cycle, without affecting the viability of the growing follicle. In case of inadequate follicular growth related to treatment with LHRH-antagonists, low dose and short term administration of gonadotrophin or other trophic compounds will compensate for these
25 effects. Subsequently, by stopping the LHRH-antagonist treatment, it is possible to let the normal ovulation occur or to induce ovulation by exogenous manipulation, if necessary. Ovulation induction was induced by

the administration of standard HCG or by administration of LHRH and/or LHRH agonistic analogs.

These described treatment alternatives are a departure from existing protocols, since they are possible only if preceded by treatment for LH-
5 surge-control with an LHRH-antagonist. In animal and clinical studies with Cetorelix it was shown that the responsiveness of the pituitary to LHRH or agonistic analogs is preserved under these conditions of treatment. Without this treatment, the pituitary cannot respond after agonistic pretreatment for LH-surge control due to receptor down-
10 regulation. In addition, the possible use of ovulation inducing agents other than HCG results in a reduced incidence of ovarian hyperstimulation syndrome.

On the basis of the described results, for the first time it is possible to use normal, non-gonadotropin-stimulated cycles for assisted
15 reproduction techniques, including sperm injections, by determining the time of ovulation by the duration and dose of Cetorelix given. Especially in conjunction with the method of ICSI (Intra-Cytoplasmatic-Sperm-Injection) this antagonist-dependent treatment modality facilitates the inclusion of in-(sub-)fertile males into this kind of fertility treatment. Due
20 to the direct injection of male gametes capable for fertilization, this method has a high success rate and hence, allows the harvest of only one follicle for fertilization. In addition, the use of LHRH-antagonists like Cetorelix in the described manner relieves the patient from severe ovarian hyperstimulation and significantly reduces the costs of a treatment cycle.

25 LHRH-antagonists of the invention can be used in combination with assisted reproduction techniques, especially the extracorporal fertilization, e.g. the in-vitro fertilization and the sperm injection techniques.

Compounds with the desired LHRH-antagonistic activity include a LHRH-analog such as Ganirelix, Antarelix, Antide, Azaline B, Ramorelix, A-76154, Nal-Glu, 88-88, in particular Cetrorelix or a structure-truncated peptide with LHRH-antagonistic activity or a peptideomimetic with

5 LHRH-antagonistic activity, for example D-23980 and D-24824, or a bicyclic (1-4. 4-10) LHRH analog with antagonistic activity.

LHRH-antagonists of the invention can be subcutaneously administered in dosage amounts of about 0.001-0.2 mg/kg.

Both dosing schedules demonstrate the prevention of any premature

10 LH surge. After both posologies good fertilization rates have been obtained with good follicle and oocytes quality. Pregnancy rates are good after both treatments. To date, a total of 44 healthy babies are born following both treatments.

The single dose regimen requires only one single injection of 3 ml.

15 This has to be regarded as being convenient for the patient. So far, duration of effect to prevent a premature LH surge is up to 6.5 days. After 3 days, monitoring of hormones is advisable in order to apply a second injection in case of a low responder to HMG with prolonged administration of HMG, and if an increase of LH values is seen.

20 The multiple dose schedule requires daily injections of 1 ml for 3 to 7 days, sometimes up to 10 or 14 days. This is not as convenient as a single or dual injection. On the other hand, regular monitoring of the hormones is not required and the application of HCG could even be extended if required in rare cases.

25 In summary, from a medical point of view, both treatments show comparable efficacy, safety and practicability, therefore each gynecologist should have the possibility to decide upon the dosing schedule with respect

to the situation observed in each single patient.

The results of a phase II clinical trial are shown in Table I.

A total of 235 patients were treated.

No premature LH surge was seen in any patient undergoing
5 COS/ART treated with either multiple doses of 0.25 mg or higher or a
single dose of 3 mg or higher. During multiple dosing, the mean days of
Cetrorelix application is 6 days. 25 babies were born by the end of May
1996 (7 following multiple doses; 18 following single/dual doses).

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Table I

| Cetrorelix Development Controlled Ovarian Stimulation (COS/ART) | | | | |
|--|------------------|--|---|------------------------|
| | Subj. Nos. | Phase | Dose/Day (mg) | Posology (days) |
| | 14 | II/proof concept | 3 | 3-10 |
| | | | | |
| | 19 | II/proof concept | 1 | 3-10 |
| | 11 | II/proof concept | 0.5 | 3-10 |
| | | | | |
| | 32 30 (28) | II/ dose finding/ minimal effective dose | 0.5 0.25 min. effect. dose 0.10 no effect. dose | 3-7/14 |
| | | | | |
| | 21 | II/proof concept | 5 | 1 or 2 |
| | 18 | II/proof concept | 3 | 1 or 2 |
| | | | | |
| | 32 30 | II/dose finding/ minimal effective dose | 3 min. effective dose 2 no effect. Dose | 1 1 |
| | | | | |
| SUM Phase II | 235 finished | | 71 pregnancies (30%) 16 pregnancies (ongoing) | 44 healthy children |

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The main advantages in controlled ovarian stimulation (COS/ART) with Cetrorelix are:

1. New therapeutic principle

- a) Prevention of premature LH-surges
- b) Uniform and continuous follicular synchronization
- c) Uniform and continuous estradiol development
- d) Very low LH-values for optimal follicular development

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2. Short term treatment of 3 to 7 days to max 14 days
 - a) Short-term exposure during follicular development
 - b) Low medication exposure during follicular development
3. No flare-up but immediate hormonal response
- 5 4. No pretreatment for 14 to 21 days before start of HMG needed
5. Fits well into normal menstrual cycle with
 - a) No modification of physiological menstrual cycle pattern or
 - b) No hormonal withdrawal syndromes before stimulation
6. No or only ultrashort-term residual effects after ovulation induction
- 10 7. No residual effects during and following embryo transfer
8. No ovarian cyst formation before start of stimulation
9. Reduction of HMG.

Table II (flow chart) shows an example on a typical treatment start and duration of HMG and Cetorelix in patients to undergo controlled

- 15 ovarian superovulation for ART.

Example

238 patients were treated with Cetorelix by subcutaneous injection of Cetorelix Acetat-Lyophilisat.

134 patients were treated with multiple doses and 104 patients with 5 single or dual doses. The multiple doses are 0.25 mg/day or higher. The single dose was 3 mg or higher. No premature LH surge was seen in any patient undergoing controlled ovarian superovulation for assisted reproduction technology (COS/ART) treated with these dosages. Multiple doses were applied for 3 to a maximum of 10 days dependent on follicular 10 development.

As a result 71 pregnancies were obtained = 30.0%

38 of 134 following the multiple doses regimen = 28.4%

33 of 104 following the single/dual dosage regimen = 31.7%

Following treatment 44 babies were born that means 15 following 15 multiple doses and 29 following single/dual doses. 16 pregnancies are still ongoing. Figure 1 shows this in particular.

Figure 1 shows an absolute prevention of any premature LH surge. Furthermore, FSH secretion is maintained at a natural level and therefore the individual estrogen development is not affected.